Remarks

Claims 1-6, 8, and 10-20 were pending in the subject application. By this Amendment claims 1, 5, 8, 13, 15 and 19 have been amended; claims 2, 10 and 16 have been cancelled; and new claim 21 has been added. Thus, claims 1, 3-6, 8, 11-15 and 17-21 are now presented for consideration by the Examiner.

Support for these amendments and new claims can be found throughout the subject specification including, for example, on page 1, lines 31-32. The amendments to the claims have been made in an effort to lend greater clarity to the claimed subject matter and to expedite prosecution. These amendments should not be taken to indicate the applicant's agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

The subject invention provides a unique material (hereinafter "micrin") that has the remarkable ability to reduce organ or tissue mass (including non-gonadal organs) in a mammal. Micrin is an endogenous material that can be obtained from a nominal 10-30 kD molecular weight fraction of ovarian venous blood plasma. Those skilled in the art generally expect that endogenous endocrine materials generally increase organ size (see application as filed, page two). Thus, it is quite unexpected (and highly advantageous) that the current applicant has discovered a novel, endogenous material that can be used to reduce organ size.

Claims 1, 8 and 15 have been rejected under 35 U.S.C. §102 (b) as being anticipated by Hart (*Toxicology*, 61(2):185-194 (1990)). To the extent that this ground for rejection might be applied to the amended claims, the applicant respectfully traverses this ground for rejection because the Hart reference does not disclose the current applicant's specific material or its use.

The Hart reference does not disclose an endogenous product having the characteristics as the composition now claimed. As explained by Dr. Hart in his Expert Declaration under 37 CFR §1.132 (copy enclosed), micrin has very different characteristics than the material described in the cited Hart reference. In his Expert Declaration, Dr. Hart provides objective scientific facts establishing that the composition claimed in the current case is not the same as the composition described in the Hart reference. Certainly, the statements of Dr. Hart should be given careful consideration and great

credence in view of the fact that he is a recognized expert in the field and the author of the cited Hart reference.

As indicated by Dr. Hart in his Expert Declaration, the cited Hart reference only discloses clomiphene. Clomiphene is a non-endogenous, synthetic compound having a molecular weight below 500 daltons. In contrast, the current claims are drawn to an entirely separate material (micrin) that is an endogenous compound, inducible by clomiphene, and which has a molecular weight that is significantly higher (obtained from a nominal 10 kD -30 kD fraction) than clomiphene.

It is a basic premise of patent law that, in order to anticipate, a single prior art reference must disclose within its four corners, each and every element of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra*; *Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

The outstanding Office Action notes a statement by Hart referring to a "decrease" in organ weights (bottom of page 192). It is acknowledged that clomiphene has this effect – that is now recognized as being partly due to its inducing micrin. Please note that, earlier on page 192, the Hart reference states that: "[t]he increases in the organ weights observed when hexoestrol was administered alone were largely prevented in a dose-dependent manner by pretreatment with clomiphene." In the next paragraph Hart explains further:

> Granted a mediating or co-operative pituitary role in hexoestrol-induced uterine, hepatic and adrenal weight gains, it can be speculated that the observed effects of clomiphene are due to competitive antagonism at some point along the hypothalamic-pituitary axis. This would imply that clomiphene acts centrally to prevent, for example, the possible increase in growth hormone secretion implicated in the hexoestrol-induced liver enlargement. A single site of action would account for the rather similar dose-dependent pattern of stepwise decrements in organ weights seen in Experiment 1 (Fig. 1). Clomiphene depresses the uptake of oestradiol by the anterior pituitary and anterior hypothalamus. (Citation omitted).

The paragraph quoted above immediately precedes Hart's statement about decreased organ weights. It is clear from this quoted paragraph that Hart envisaged that clomiphene was an antagonist to estrogen (whether endogenous or exogenous); he did not envisage that clomiphene was inducing a down-regulator (i.e. micrin). This is even clearer from the last sentence of the following paragraph (top of page 193):

"Antagonism of endogenous oestrogen may be involved here, as clomiphene is ineffective in reducing the liver weight in ovariectomised mice." (Citation omitted)

The Office Action characterizes the applicant's claims as "product-by-process." It should be noted that, although the applicant's claims include an identification of the source of the product, a prior art rejection is proper only if there is a rationale for believing that a prior art reference discloses the claimed material. The clomiphene described in the Hart reference is not endogenous, and has a substantially lower molecular weight than the claimed composition. Accordingly, there is no rationale for concluding that the currently claimed composition is the clomiphene disclosed by Hart.

Because the Hart reference does not disclose the applicant's claimed composition, an anticipation rejection is not proper. Accordingly, the applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. §102(b).

Claims 1-5, 8, 10-13 and 15-19 have been rejected under 35 U.S.C. §102(b) as being anticipated by diZerega (U.S. Patent No. 4,734,398) or, in the alternative, under 35 U.S.C. §103(a) as obvious over diZerega. The applicant respectfully traverses this ground for rejection because the diZerega reference does not disclose or suggest the material (or its use) claimed by the current applicant.

The diZerega reference discloses a follicular regulatory protein (FRP), which suppresses ovarian response to gonadotropins. As noted by Dr. Hart in his Expert Declaration,

> 7. diZerega discloses "Follicular Regulating Protein" (hereinafter FRP). FRP is only detectable immediately downstream of an ovary which is just about to ovulate, and is not concurrently detectable downstream of the contralateral anovulatory ovary. Micrin is detectable six-days post-oestrus (i.e. post-ovulation), downstream of both ovaries, concurrently. FRP is not detectable in anovulatory individuals. Micrin is detectable in anovulatory individuals. FRP is not detectable in peripheral blood. Micrin is detectable in peripheral blood.

8. Micrin activity is detectable in blood plasma at a time (after ovulation) and from places (downstream of anovulatory ovaries and from peripheral blood) when and where FRP activity is not detectable (diZerega, Example One, Column 8-12, notably Column 10, lines 52-60 and Column 11, lines 61-66).

9. FRP is exclusively ovarian in origin: it is secreted by granulosa cells in the ovary (see Column 11, lines 55-60 and Column 28, line 65). Micrin is produced by the ovaries and testes, and by other organs.] p.2

10. FRP inhibits gonadotropin action in the ovary. FRP therefore suppresses gonadotropin-induced regrowth of juvenile rat ovaries previously shrunken by hypophysectomy. Micrin reduces, in normal adult female rats, the masses of organs such as the heart and kidneys which are uninfluenced by gonadotropins and remote from the ovaries. It is unlikely that FRP has a downregulatory effect on such organs as the heart and kidneys, since it is an intra-ovarian gonadotropin inhibitor which does not appear in peripheral blood.

√ 11. I infer from Fig. 18 of diZerega that FRP is not induced by clomiphene.

As explained in Dr. Hart's Expert Declaration, the currently claimed composition is readily distinguishable from FRP. Dr Hart notes, for example, that unlike FRP, micrin is detectable six days post-oestrus (*i.e.*, post-ovulation), downstream of both ovaries, concurrently. Also, as noted above, and unlike FRP, micrin is inducible by clomiphene. Produced by the ovaries and testes, as well as other organs, micrin is detectable not only in anovulatory individuals but also in peripheral blood. Accordingly, the claimed composition is clearly <u>not</u> FRP.

As noted above, for an anticipation rejection to be proper, a single prior art reference must disclose, within its four corners, each and every element of the claimed invention. In *Dewey & Almy Chem. Co. v. Mimex Co.*, Judge Learned Hand wrote:

> No doctrine of the patent law is better established than that a prior patent . . . to be an anticipation must bear within its four corners adequate directions for the practice [of the subsequent invention] . . . if the earlier disclosure offers no more than a starting point . . . if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation. 124 F.2d 986, 990; 52 USPQ 138 (2nd Cir. 1942).

The present invention is directed to an endogenous material inducible by clomiphene that is wholly separate from the FRP disclosed by diZerega. Because the diZerega reference does not

disclose, within its four corners, a composition having the characteristics recited in the current claims, an anticipation rejection is improper.

Nor is the subject invention obvious in view of diZereqa. As the Examiner is undoubtedly aware, it is well established in patent law that in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making and practicing the invention, in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1531, (Fed. Cir. 1988). The diZerega reference does not disclose or suggest micrin nor does it teach using micrin to reduce organ mass. In fact, diZerega merely discloses FRP activity in inhibiting gonadotropin-induced re-growth in preshrunk ovaries.

As Dr. Hart states in his Declaration, "[i]t is unlikely that FRP has a downregulatory effect on organs generally, since it is an intra-ovarian gonadotropin inhibitor which does not appear in peripheral blood." In view of the foregoing remarks and the Dr. Hart Declaration submitted herewith, the applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) and in the alternative §103(a).

Claims 1-6, 8 and 10-20 have been rejected under 35 U.S.C. §103(a) as obvious over diZerega. The applicant respectfully traverses this ground for rejection because the diZerega reference neither teaches nor suggests the applicant's material or its use.

The shortcomings of the diZerega reference are as described above. diZerega only discloses FRP, whose characteristics and function are entirely different from those of micrin. Nothing in the diZerega reference would have led the skilled artisan to the unique material (micrin) and methods of the subject application.

A finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, it is only the applicant's disclosure that provides such a teaching, and the applicant's disclosure cannot be used to reconstruct the prior art for a rejection under 35 U.S.C. §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112

> USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

The mere fact that the purported prior art could have been modified or applied in a manner to yield the applicant's invention would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Moreover, as expressed by the CAFC, to support a §103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art . . . ." *In re Dow Chemical Co., supra* at 1531. In the diZerega reference, one finds neither.

The diZerega reference does not disclose or suggest a material that is inducible by clomiphene nor does it disclose a material that can reduce organ mass generally. Rather, diZerega only provides FRP, a material that is not induced by clomiphene and only appears to affect ovaries and their response to gonadotropins. Thus, the diZerega reference does not describe, teach, nor suggest a material having the unique characteristics of the claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103 based on diZerega is respectfully requested.

In view of the foregoing remarks and the amendments above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicant also invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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DRS/la

Attachment: Declaration of Dr. John Ernest Hart Under 37 CFR §1.132